Published in final edited form as:
Neuron. 2009 August 13; 63(3): 287–303. doi:10.1016/j.neuron.2009.06.026.

The Role of Apolipoprotein E in Alzheimer's Disease

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Abstract

The ε4 allele of apolipoprotein E (*APOE*) is the major genetic risk factor for Alzheimer's disease (AD). Although there have been numerous studies attempting to elucidate the underlying mechanism for this increased risk, the manner in which apoE4 influences AD onset and progression has yet to be proven. However, prevailing evidence suggests that the differential effects of apoE isoforms on Aβ aggregation and clearance play the major role in AD pathogenesis. Other potential mechanisms, such as the differential modulation of neurotoxicity and tau phosphorylation by apoE isoforms as well as its role in synaptic plasticity and neuroinflammation, have not been ruled out. Inconsistent results among studies have made it difficult to define whether the *APOE* ε4 allele represents a gain of toxic function, a loss of neuroprotective function, or both. Therapeutic strategies based on apoE propose to reduce the toxic effects of apoE4 or to restore the physiological, protective functions of apoE. In addition, modulation of apoE protein levels and lipidation state by low-density lipoprotein (LDL) receptor family members and ATP-binding cassette transporter A1 (ABCA1) may be useful to exploit as future therapeutic targets.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. It is characterized clinically by progressive decline in memory, executive function, language, and other areas of cognition. Pathologically, there is formation of amyloid plaques and neurofibrillary tangles in the brain, as well as neuronal loss, synaptic loss, brain atrophy, and inflammation. Accumulation of the amyloid-β (Aβ) peptide, the major component of amyloid plaques, is hypothesized to initiate a pathogenic cascade that eventually leads to AD (Hardy and Selkoe, 2002). The sequential proteolytic processing of amyloid β precursor protein (APP) by β-secretase and γ-secretase produces several A species, including the most abundant 40 amino-acid species (Aβ40) and a number of minor species, including Aβ42 (Steiner and Haass, 2000). Aβ is produced by all cells throughout life, with highest levels made by neurons. The majority of extracellular Aβ is generated through the endocytosis of APP into the endocytic compartment, where both secretases can optimally produce A (Cirrito et al., 2008; Koo and Squazzo, 1994). Although strong genetic and biochemical evidence suggests that an increase in total A production, an increase in the ratio of Aβ42 to Aβ40, or generation of a mutant form of Aβ with greater amyloidogenic propensity are the main mechanisms for the rare early-onset forms of autosomal-dominant familial AD,

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cerebral amyloid angiopathy (CAA), or a combination of both disorders, these are probably not the major pathogenic mechanisms underlying the more common late-onset AD (Haass and Selkoe, 2007; Tanzi and Bertram, 2005). Defects in the clearance of brain Aβ by cellular uptake or transport across the blood-brain barrier might underlie many cases of sporadic AD (Selkoe, 2001; Zlokovic, 2008). In addition, increased Aβ aggregation influenced by Aβ binding molecules may also play an important role. Although non-genetic environmental factors, such as education and physical activity, may affect the risk of sporadic AD, twin studies strongly suggest that genetic factors play a critical role in late-onset AD (Gatz et al., 2006). While many putative susceptibility genes for AD have been reported, the only strongly confirmed genetic risk factor across many studies for early and late-onset AD is apolipoprotein E (*APOE*) genotype, with the ε4 allele being an AD risk factor and the ε2 allele being protective (Corder et al., 1993; Strittmatter et al., 1993a). Strong evidence suggests the major mechanism by which apoE influences AD and CAA is via its effects on Aβ metabolism. However, the details of this process as well as the role apoE plays in non-Aβ mediated mechanisms in AD pathogenesis remain to be fully clarified.

Physiological Function of ApoE

The human apoE protein is a 299 amino acid glycoprotein with variable levels of posttranslational sialylation through O-linked glycosylation at the threonine 194 residue (Wernette-Hammond et al., 1989). ApoE is expressed in several organs with the highest expression in the liver, followed by the brain. Non-neuronal cells, mainly astrocytes and to some extent microglia, are the major cell types that express apoE in the brain (Grehan et al., 2001; Pitas et al., 1987). However, neurons can also produce apoE under certain conditions, albeit at much lower levels than astrocytes (Xu et al., 1999; Xu et al., 2006). ApoE functions as a ligand in receptor-mediated endocytosis of lipoprotein particles. In plasma, apoE proteins are present on lipoproteins in association with other apolipoproteins, whereas in the brain apoE and 2 other apolipoproteins, apoJ and apoA-1, are predominantly present on distinct high density-like lipoprotein particles (Fagan et al., 1999; Pitas et al., 1987). Unlike plasma HDL that contains apoA-1 as its major apolipoprotein, the predominant apolipoprotein of HDL in the central nervous system (CNS) is apoE (Pitas et al., 1987). Although HDL-like lipoproteins are the only lipoproteins in the central nervous system (CNS), their role in CNS lipid and cholesterol homeostasis is not clearly defined. After receptor-mediated endocytosis of apoE-containing lipoprotein particles by low-density lipoprotein (LDL) receptor family members, apoE may be either degraded or recycled back to the cell surface (Rensen et al., 2000). Cholesterol released from apoE-containing lipoprotein particles is used to support synaptogenesis and the maintenance of synaptic connections (Pfrieger, 2003). Whether apoE-containing lipoproteins play a major role in supporting synaptogenesis and maintenance of synaptic connections *in vivo* in the uninjured brain has not yet been proven, as several studies have shown that the brain of apoE knock-out mice for the most part appears normal in the absence of injury (Anderson et al., 1998; Fagan et al., 1998).

Other Apolipoproteins in the Brain

In addition to apoE, several other apolipoproteins, including apoA-I, apoA-II, apoA-IV, apoD, apoE, apoH, and apoJ, are found in the brain. Among them, the potential roles of apoA-I and apoJ in Aβ fibrillogenesis and clearance have been investigated (Ladu et al., 2000a). ApoA-I is the major apolipoprotein in plasma HDL, mediating reverse cholesterol transport. Although it is also found in the CSF, apoA-I is not synthesized in the brain but transported across the blood-brain barrier (BBB). In contrast, apoJ (also known as clusterin) is expressed in neurons and astrocytes and its expression in astrocytes is strongly induced

following injury (Charnay et al., 2008). The presence of brain apolipoproteins on distinct particles in the CNS may be due to their differences in biogenesis. Both apoA-I and apoJ are known to bind to Aβ and prevent Aβ aggregation and toxicity *in vitro* (Ghiso et al., 1993; Koldamova et al., 2001; Paula-Lima et al., 2009). However, such *in vitro* findings apparently contradict with *in vivo* results obtained with apoA-I and apoJ knock-out mice. ApoA-I deficiency did not alter amyloid pathology (Fagan et al., 2004), while apoJ deficiency significantly reduced fibrillar amyloid plaque formation and neuritic toxicity in a mouse model of amyloidosis (DeMattos et al., 2002). More studies are required to further elucidate the relative contribution of the effects of apoAI and apoJ on Aβ fibrillogenesis and metabolism *in vivo*.

Genetics of ApoE in AD

The human apoE gene contains several single-nucleotide polymorphisms (SNPs) distributed across the gene (Nickerson et al., 2000). The most common three SNPs lead to changes in the coding sequence and result in the three common isoforms of apoE: apoE2 (cys112, cys158), apoE3 (cys112, arg158), and apoE4 (arg112, arg158). Although the three common isoforms differ by only one or two amino-acids at residue 112 or 158, these differences profoundly alter apoE structure and function (Mahley et al., 2006). After immunoreactivity of apoE in amyloid plaques was first reported (Namba et al., 1991; Wisniewski and Frangione, 1992), the ε4 allele of the *APOE* gene was discovered to be a strong genetic risk factor for AD (Corder et al., 1993; Strittmatter et al., 1993a). Since then, numerous studies have confirmed that possession of the ε4 allele is the strongest genetic risk factor for both AD and CAA, or a combination of both disorders (Bertram et al., 2007; Farrer et al., 1997). As compared to individuals with no ε4 alleles, the increased risk for AD is 2–3 fold in people with one ε4 allele and about 12-fold in those with two ε4 alleles (Bertram et al., 2009; Roses, 1996). The apoE ε4 allele is also associated with an earlier age of AD onset (Gomez-Isla et al., 1996; Roses, 1996). However, in certain ethnic groups, the apoE ε4 allele seems to have either a weaker effect or no clear effect on AD (Farrer et al., 1997; Kalaria et al., 2008; Mayeux, 2003; Tang et al., 1998). These results suggest that other genetic and environmental factors may also contribute to AD risk in certain ethnic groups. Finally, it is important to note that the ε2 allele of apoE is associated with a lower risk for AD (Corder et al., 1994; Farrer et al., 1997).

While the effect of the ε4 allele on the risk and age of onset for AD is generally consistent in most studies, there have been numerous conflicting reports regarding whether different apoE alleles influence the rate of cognitive decline following dementia onset (Asada et al., 1996; Craft et al., 1998; Frisoni et al., 1995; Growdon et al., 1996; Hoyt et al., 2005; Kurz et al., 1996). Some studies suggest that the effect of the ε4 allele on cognitive decline is stronger in the earlier clinical stages of disease and is weaker during the later and more severe clinical stages (Cosentino et al., 2008; Juva et al., 2000). Understanding whether apoE plays a mechanistic role in the progression of AD is an important question to address in the future and will provide further insights into its pathophysiological role in AD. In addition, a more accurate prediction of disease progression based upon ε4 allele status may allow for better clinical trial design. If the ε4 allele does differentially affect the progression and response to therapies, it will be critical to subdivide subject groups and analyze the rate of cognitive decline separately according to apoE genotype.

Effects of ApoE on Aβ Aggregation

Human studies

Although several reasons may underlie the apoE isoform-specific effect on the risk of developing AD (Figure 1), convincing evidence suggests that the physical interaction of

apoE with Aβ plays an important role in AD pathogenesis. Based on the strong association between apoE and Aβ the brain (Naslund et al., 1995), it was hypothesized that apoE may function as an Aβ-binding protein that induces a pathological β-sheet conformational change in Aβ (Wisniewski and Frangione, 1992). Initial histopathological studies investigating the relationship between amyloid plaques and apoE isoforms demonstrated a positive correlation between plaque density and apoE ε4 allele dose (Rebeck et al., 1993;Schmechel et al., 1993). However, several subsequent studies reported conflicting findings (Benjamin et al., 1995;Heinonen et al., 1995;Itoh and Yamada, 1996;Landen et al., 1996b). Nonetheless, a more conclusive study with many more subjects strongly suggested that apoε4 allele dosage is associated with increased neuritic plaques in AD (Tiraboschi et al., 2004). Importantly, if the overall effect of apoE4 is to accelerate the onset of Aβ deposition into amyloid plaques, one would expect to see the largest effect of apoE4 on brain amyloid deposition in the late-middle age period in subjects who are still cognitively normal but who are “at risk” to develop AD. In fact, in a large CSF study of cognitively normal middle age people, CSF Aβ42 was apoE4-dose dependently lower (Sunderland et al., 2004). Since people with brain amyloid deposition have low CSF Aβ42 (Fagan et al., 2006), this strongly suggests that amyloid deposition on average is beginning earlier in apoE4-positive subjects. This finding has now been confirmed more directly in a study that showed cognitively normal subjects had an ε4 dose-dependent increase in fibrillar Aβ burden in brain as detected with an amyloid imaging agent (Reiman et al., 2009). On the other hand, the effect of the apoE2 isoform on AD neuropathology has not been thoroughly investigated, in part, due to the relative rarity of apoE2-positive participants. It remains unclear whether apoE2 exerts its protective effect through modulating Aβ aggregation or an alternative mechanism that is independent of amyloid plaque formation (Berlau et al., 2009).

In vitro Aβ binding studies

Following initial genetic and neuropathological findings from human studies, many groups investigated the ability of apoE isoforms to bind Aβ and subsequently influence its aggregation process *in vitro*. Initially, it was demonstrated that lipid-free apoE formed SDS-stable complexes with Aβ, and that apoE4 bound to Aβ more rapidly than apoE3 (Sanan et al., 1994; Strittmatter et al., 1993b). However, subsequent studies reported that lipid-associated apoE2 and apoE3 formed SDS-stable complexes with Aβ to a much greater extent than apoE4 (Aleshkov et al., 1997; LaDu et al., 1994; Yang et al., 1997). Most studies demonstrate that the efficiency of complex formation between lipidated apoE and Aβ follows the order of apoE2 > apoE3 ≫ apoE4 (Tokuda et al., 2000). Since the binding efficiency of apoE isoforms to Aβ correlates inversely with the risk of developing AD, it has been hypothesized that apoE2 and apoE3 may enhance the clearance of Aβ, compared to apoE4. Residues 12–28 of Aβ appears to contain the binding site for apoE (Strittmatter et al., 1993a; Strittmatter et al., 1993b) and this region has been used to block the interaction between apoE and Aβ (Ma et al., 1996; Sadowski et al., 2006).

In vitro Aβ aggregation studies

Given the strong genetic evidence and the isoform-specific difference in the interaction of apoE with Aβ, the effect of apoE isoforms on Aβ aggregation has been investigated extensively *in vitro*. One study demonstrated that all three apoE isoforms promoted Aβ42 fibrillization, with the effect being more enhanced with the apoE4 isoform and least with apoE2 (Ma et al., 1994). Subsequently, others also found that apoE4 was more efficient than apoE3 at increasing Aβ40 aggregation (Castano et al., 1995; Wisniewski et al., 1994). These findings are apparently consistent with the increased amyloid plaque load in subjects with the apoE ε4 allele. However, human genetic and histological data do not exclude the possibility that all three apoE isoforms are inhibitors of Aβ aggregation, with apoE4 being the least effective at inhibition. Indeed, other studies reported that human apoE isoforms

decreased Aβ fibrillogenesis *in vitro* by interfering with Aβ nucleation (Beffert and Poirier, 1998; Evans et al., 1995; Webster and Rogers, 1996; Wood et al., 1996). Conflicting results between numerous *in vitro* studies may be due to the differences in apoE and Aβ preparations or other factors discussed below.

Difference in apoE preparations

The formation of heterogeneous multimeric forms of apoE, the diverse assembly states of apoE, and the variable levels of oxidation in apoE may affect the binding properties of apoE to Aβ and other apoE binding proteins, including apoE receptors. More importantly, the different extent of apoE lipidation seems likely to be responsible for the contradictory results among various *in vitro* studies. Since considerable conformational differences exist between lipid-free and lipid-bound forms of apoE (Blacklow, 2007), the presence of lipids leads to alterations in the binding properties of apoE with Aβ as well as other proteins (Dergunov et al., 2000; Ljungberg et al., 2003). Since most *in vitro* studies have used non-physiological preparations of lipid-free apoE, the implications of such findings to the *in vivo* environment remain uncertain. It is more desirable to use apoE prepared in a condition that preserves its native lipoprotein particle structure found in the brain to best understand its role in the CNS and in Aβ metabolism.

Aβ40 versus Aβ42

Several recent studies suggest that Aβ40 and Aβ42 may have opposing effects on Aβ aggregation *in vivo* (Kim et al., 2007; McGowan et al., 2005). Given these emerging data, results from Aβ40 *in vitro* aggregation experiments may need to be interpreted somewhat differently. Interestingly, there have been several reports suggesting that Aβ40 preferentially aggregates in an apoE4 gene dose-dependent manner in AD subjects (Gearing et al., 1996; Ishii et al., 1997; Mann et al., 1997). Although the apparent differential effects on Aβ40 and Aβ42 aggregation by apoE4 might be simply attributed to the increased CAA in apoε4 subjects, careful immunohistochemical analyses of plaques using Aβ40 or Aβ42 specific antibodies suggest that increased CAA in ε4-positive subjects does not entirely account for the preferential Aβ40 deposition (Gearing et al., 1996; Mann et al., 1997). It is conceivable that ApoE4 may be able to induce a conformational change in Aβ40, which either renders it into an Aβ42-like structure or generates a distinctly polymorphic ApoE4-Aβ40 complex with higher aggregation propensity. The differential effects on Aβ aggregation by apoE isoforms warrant further investigation.

Difference in Aβ preparations and aggregation conditions

Inconsistent reports regarding the effect of apoE on Aβ aggregation may also be attributable to the inherent issues with synthetic Aβ preparations. Characteristics of Aβ fibrillogenesis, such as lag time and rate of aggregation, can vary considerably between apparently identical samples due to the use of starting materials that contain heterogeneous mixtures of monomers and oligomers. Since apoE isoforms have differential binding affinities to different aggregation intermediates, it is critical to use well-defined single Aβ species as a starting material. One of the most critical parameters is the concentration of Aβ and apoE used in the aggregation assay. Almost all Aβ *in vitro* fibrillogenesis experiments with apoE isoforms have been performed with non-physiologically high μM concentrations of Aβ Such high concentrations may artificially cause Aβ40 to aggregate without an Aβ42 seeding nucleus, despite the fact that Aβ40 has an anti-amyloidogenic effect *in vivo* (Kim et al., 2007). Therefore, the *in vivo* implication of findings from such non-physiological conditions is not clear. Most importantly, nearly all studies have used a high molar ratio of Aβ to apoE, *in vitro* conditions that are opposite to what is found *in vivo* where the apoE/Aβ molar ratio is 10–30. To better understand the effect of apoE isoforms on Aβ aggregation, further experiments should be performed with apoE and Aβ prepared to match *in vivo* conditions.

In vivo animal data

Although *in vitro* studies investigating the interaction between apoE and Aβ have been informative, the *in vivo* environment surrounding apoE and Aβ in the brain may be very different from the artificial settings of *in vitro* experiments. Initial studies using the PDAPP and Tg2576 APP transgenic mouse models that develop Aβ deposition demonstrated that the lack of murine apoE resulted in a significant decrease in Aβ deposition, along with an almost complete lack of true amyloid plaques and neuritic dystrophy (Bales et al., 1997; Holtzman et al., 2000; Holtzman et al., 1999). Furthermore, in the PDAPP mouse model, the anatomical pattern of Aβ deposition was markedly different (Fagan et al., 2002; Irizarry et al., 2000). These results make it evident that mouse apoE plays a significant role in both the extent and distribution of Aβ deposition, along with its associated damage to neurites. Following these initial studies with apoE knock-out mice, several lines of transgenic mice were generated to study the role of human apoE isoforms in AD pathogenesis (Raber et al., 1998; Sun et al., 1998; Xu et al., 1996). The expression of human apoE isoform transgenes in PDAPP mice resulted in a marked delay in the deposition of Aβ and formation of neuritic plaques, compared to PDAPP mice expressing murine apoE or no apoE (Fagan et al., 2002; Holtzman et al., 2000; Holtzman et al., 1999). Interestingly, the human apoE transgenic mice display an isoform-specific pattern of Aβ deposition in the hippocampus, with apoE4 mice having increased levels of Aβ deposits and more thioflavine-S positive plaques than apoE3 mice (Fagan et al., 2002; Holtzman et al., 2000). Other studies using transgenic mice that possess different human apoE transgenes also demonstrate an isoform-specific difference (E4>E3) in Aβ deposition (Buttini et al., 2002; Dolev and Michaelson, 2004).

Although transgenic mouse models have been useful for investigating the role of human apoE isoforms in AD, the generation of apoE knock-in mice that express human apoE isoforms under the control of endogenous mouse regulatory elements allows one to examine the role of each isoform under more physiological conditions (Hamanaka et al., 2000; Sullivan et al., 1997; Sullivan et al., 1998). When apoE3 and apoE4 knock-in mice were bred to the Tg2576 mice, apoE3 and apoE4 delayed the onset of Aβ deposition relative to mouse apoE and apoE4 mice had significantly more amyloid deposition and CAA than apoE3 mice (Fryer et al., 2005b). Recently, PDAPP mice bred to apoE2, E3, and apoE4 knock-in mice demonstrated a clear isoform-dependent (E4>E3>E2) effect on Aβ accumulation (Bales et al., 2009). It is clear that elucidating what the underlying *in vivo* mechanisms are for the apoE isoform-mediated difference in Aβ accumulation is critical for relating these findings to the pathogenesis of AD.

Several key questions remain to be further addressed using *in vivo* models that develop Aβ accumulation. The somewhat rudimentary but important question still exists as to whether it is better to increase or decrease human apoE levels (regardless of isoform) in order to reduce Aβ levels. A preliminary study suggests that APP transgenic mice heterozygous for apoE3 have more deposited Aβ in the brain in comparison to mice with two copies of the apoE3 allele (DeMattos, 2004). In addition, intracerebral administration of a lentivirus expressing human apoE2 into the brains of PDAPP mice has shown that gene delivery strategies may be useful in decreasing Aβ burden (Dodart et al., 2005). Analyzing whether, and to what extent, altering human apoE level affects Aβ pathology will help determine whether targeting apoE levels may be a viable therapeutic option for influencing Aβ levels and toxicity, and ultimately treating AD.

Effects of ApoE on Aβ Clearance

In addition to the effects on fibrillogenesis, there is evidence that apoE alters both the transport and metabolism of Aβ in the brain. The effects of apoE isoforms on APP processing and Aβ production have been investigated in cell culture systems. A few studies

suggest that lipid-poor and lipid-free apoE4 enhance Aβ production by increasing LRP1- and ApoER2-mediated APP endocytosis (He et al., 2007; Ye et al., 2005). However, others found no clear evidence for isoform-specific effects on APP processing (Biere et al., 1995; Cedazo-Minguez et al., 2001; Irizarry et al., 2004). In addition, there is no convincing data suggesting apoE isoforms have differential effects on the production of Aβ *in vivo*. Regardless of its effect on Aβ production, apoE seems to play an important role in the clearance of Aβ through several plausible mechanisms (Figure 2). ApoE-containing lipoprotein particles may sequester Aβ and modulate the cellular uptake of an apoE-Aβ complex by receptor-mediated endocytosis. Alternatively, apoE may modulate Aβ removal from the brain to the systemic circulation by transport across the blood-brain-barrier. Several *in vitro* studies have demonstrated that human apoE facilitates the binding and internalization of soluble Aβ by various types of neuronal cells (Beffert et al., 1998, 1999a; Cole and Ard, 2000; Nielsen et al., 2008; Yamauchi et al., 2002; Yamauchi et al., 2000; Yang et al., 1999). Though some of these studies did observe apoE isoform-dependent differences in the extent of Aβ cellular uptake, no overall trend emerged. Two *in vitro* studies have also demonstrated that apoE can facilitate the cellular degradation of Aβ (Jiang et al., 2008; Koistinaho et al., 2004). However, more studies are necessary to solidify whether apoE facilitates the uptake of Aβ into the various cell types found in the brain, whether this enhanced uptake occurs in an isoform-specific manner, and by what mechanism this may occur.

An issue that remains unclear is how these *in vitro* results relate to what has been observed in the *in vivo* environment, where apoE deficiency leads to a dramatic reduction in thioflavin-S positive amyloid load (Bales et al., 1999; Bales et al., 1997; Holtzman et al., 1999). Interestingly, it has been shown that in young PDAPP mice prior to the onset of Aβ deposition, that the lack of apoE may actually increases soluble Aβ levels, a finding that is consistent with cell culture data (Dodart et al., 2002; Fagan et al., 2002). This result was also demonstrated in a study where *in vivo* microdialysis was used to analyze the level of Aβ in brain interstitial fluid (ISF) (DeMattos et al., 2004). While some publications support the *in vitro* studies that suggest apoE enhances cellular Aβ uptake and degradation, one must also consider the blood-brain barrier as a potential pathway of Aβ clearance in the brain, especially via LRP1 (Zlokovic, 2008).

In the presence of human apoE, the *in vivo* clearance of Aβ has not been extensively studied. A recent study has shown that the brain to blood clearance of lipidated apoE4 in the mouse brain is significantly lower than the clearance of apoE3 and apoE2 (Deane et al., 2008). Interestingly, this trend is opposite for what is observed for the total brain levels of human apoE when the human apoE genes are expressed in knock-in mice. Therefore, whether the BBB plays a major role in regulating the levels of apoE in the brain needs to be further verified. Accumulating recent evidence strongly suggests that when human apoE is complexed with Aβ, the brain to blood clearance of Aβ is actually decreased compared to that of free Aβ (Bell et al., 2007; Deane et al., 2008; Ito et al., 2007). Furthermore, Aβ complexed to apoE2 and apoE3 is cleared out of the brain at a significantly faster rate than Aβ complexed to apoE4 (Deane et al., 2008). However, another study using different methods also looking at BBB transport of Aβ in mice expressing transgenes for either human apoE3 or apoE4 did not show any differences in the clearance of Aβ from the brain (Ji et al., 2001). Finally, an apoE4-Aβ complex present in the periphery is sequestered into brain capillaries to a greater extent than Aβ bound to apoE2 or apoE3, demonstrating that apoE4-mediated blood to brain transport of Aβ may play a role in amyloid accumulation in the brain (Martel et al., 1997). Despite these findings, more work is needed to determine the exact role that the BBB plays in mediating Aβ clearance, how apoE plays a role in this process, and whether isoform-specific effects exist.

ApoE Levels in the Central Nervous System

ApoE levels between AD cases and controls

Given the strong effect of apoE alleles on the risk of developing AD, there have been numerous studies investigating if apoE protein levels are associated with AD. Previous studies of CSF apoE levels in humans provided no clear consensus on this question (Landen et al., 1996a; Lefranc et al., 1996; Lehtimaki et al., 1995; Lindh et al., 1997; Mulder et al., 1998; Sihlbom et al., 2008). To minimize confounding factors, such as the difference in CSF collection methods and severity of disease, a subsequent study classified a large number of subjects according to clinical dementia rating (CDR) and analyzed apoE protein level in CSF collected in a standardized manner (Wahrle et al., 2007). The levels of CSF apoE were not significantly different between cognitively normal subjects (CDR 0) and those who had very mild (CDR 0.5) or mild-moderate dementia (CDR 1–2). The relationship between apoE levels in CSF and brain parenchyma is not well studied yet.

CSF apoE levels among isoforms

Although there have been many studies trying to understand the differential effects of apoE isoforms on AD pathogenesis, it is possible that the observed phenotypes are, in part, mediated by the difference in the levels of apoE proteins in the brain between isoforms. Such differences in the amount of apoE could modulate the risk for AD, as it has been demonstrated for the risk of cardiovascular mortality (Mooijaart et al., 2006). A number of studies investigating apoE protein levels in the brain and CSF in correlation with apoE genotypes have generated inconsistent results. One study reported that apoE4 accounted for 60–70% of the total apoE protein in CSF from ε3/ε4 heterozygote subjects, which contrasted with the lower proportion of apoE4 in plasma (Fukumoto et al., 2003). However, earlier studies found that CSF apoE concentrations did not vary among different apoE isoforms (Landen et al., 1996a; Lehtimaki et al., 1995). More recent studies also report that CSF apoE concentrations, measured by apoE ELISA and nephelometry, do not significantly differ among subjects with different apoE isoforms (Bekris et al., 2008; Wahrle et al., 2007).

Levels of apoE isoforms in the brain parenchyma

A number of studies investigating apoE expression and protein levels in the brain parenchyma as a function of *APOE* genotype have yielded controversial results (Beffert et al., 1999b; Bertrand et al., 1995; Bray et al., 2004; Growdon et al., 1999; Harr et al., 1996; Lambert et al., 1997; Pirttila et al., 1996). The conflicting results from brain parenchyma studies may stem from the relatively small sample size and heterogeneity in subject population, with subjects at different stages and duration of disease. Since apoE expression is transcriptionally induced by Aβ and increases with glial activation, duration and severity of disease may considerably affect apoE mRNA and protein levels. In addition, apoE levels may be artificially altered by postmortem delay (Pirttila et al., 1996). If the effect of apoE isoforms is to influence whether and when Aβ deposits, the most important time to measure it in the brain samples would be prior to the onset of Aβ deposition. This will be technically very difficult to accomplish in humans. Most importantly, prospective longitudinal studies with healthy non-demented subjects will be very informative in testing whether levels of CSF apoE, independent of *APOE* genotype, are associated with the risk of developing AD.

Mouse data

In general, human studies have certain limitations that preclude the precise analysis of apoE levels in the CNS. Thus, attention has been devoted to better characterizing apoE levels in the brain and CSF of human apoE knock-in mice (Hamanaka et al., 2000; Sullivan et al., 2004; Sullivan et al., 1997). Because these mice express apoE under the endogenous mouse

apoE promoter, protein levels should reflect the natural synthesis and metabolic rates of apoE in the mouse CNS. An initial study characterizing such mice suggested that apoE levels in the mouse brains were not significantly different among the apoE2, apoE3, and apoE4 isoforms (Sullivan et al., 2004). However, several subsequent studies were able to detect a genotype-dependent difference in apoE levels (E2>E3>E4) in the brain and CSF of apoE knock-in mice (Fryer et al., 2005a; Mann et al., 2004; Ramaswamy et al., 2005; Riddell et al., 2008; Vitek et al., 2007). If more studies confirm that an isoform-dependent difference in apoE levels is present in the brains of both humans and mice, it will be important to determine why such a phenomenon is observed. One possibility is that the clearance or degradation of apoE4 is elevated in the CNS relative to other apoE isoforms. This may be due to either differential binding of apoE isoforms to members of the LDLR family, or an intrinsic property of the apoE4 protein structure that affects its stability in the CNS. Interestingly, a recent *in vitro* study has shown that apoE4 is degraded more quickly than apoE2 or apoE3 in primary mouse astrocyte cultures (Riddell et al., 2008). It will be important to determine whether the clearance rates of apoE isoforms are different in an *in vivo* setting. It is also necessary to directly determine whether differences in apoE levels account for any effect apoE has on AD pathogenesis, as this may lead to the development of future AD therapeutics that directly target the level or stability of the apoE protein.

LDL Receptor Family Members

Given the physical interaction between apoE and Aβ, apoE-containing lipoprotein particles might alter the metabolic fate of Aβ. Since apoE-mediated Aβ clearance may be modulated by several apoE binding proteins, the potential roles of LDL receptor family members and ATP-binding cassette transporter A1 (ABCA1) in AD pathogenesis have been studied extensively (Figure 2).

Lipoprotein receptor-related protein 1 (LRP1)

LRP1 functions as an endocytic and signaling receptor with a wide expression pattern in a variety of tissues. The ligands for LRP1 include several proteins already implicated in AD pathogenesis, such as apoE, APP, Aβ, α2-macroglobulin, matrix metallopeptidase 9, and tissue-type plasminogen activator (Herz and Bock, 2002). LRP1 has been proposed to affect pathogenesis of AD by regulating Aβ catabolism and APP processing (Cam and Bu, 2006). Recently, Bu and colleagues developed conditional LRP1 forebrain knock-out mice by crossing LRP1 floxP mice with αCamKII-Cre mice (Liu et al., 2007). A series of mechanistic studies suggested that APP intracellular domain (AICD) interacts with the LRP1 promoter and suppresses its transcription. However, a subsequent study did not support a role of AICD in the transcriptional regulation of LRP1 (Tamboli et al., 2008). In contrast to the previous study, loss of γ-secretase function impaired endocytosis of LDLR by interfering with subcellular trafficking of adaptor proteins Fe65 and autosomal recessive hypercholesterolemia protein. Since the reasons for the conflicting findings remain unclear, the effects of γ-secretase on expression and processing of lipoprotein family members need to be further investigated.

Low-density Lipoprotein Receptor (LDLR)

LDLR is a cell surface glycoprotein that plays an important role in mediating the removal of cholesterol and cholesteryl ester-containing low-density lipoprotein (LDL) particles from the circulation (Brown and Goldstein, 1986; Herz and Bock, 2002). Association of apoE with lipid is required for its high-affinity binding to LDLR (Blacklow, 2007). Compared with the other isoforms, apoE2 has only 1–2% of binding affinity to LDLR and its presence is associated with hyperlipidemia in some apoE2 individuals (Ruiz et al., 2005). Direct evidence demonstrating LDLR as one of the main apoE receptors in the brain was provided

by crossbreeding LDLR knock-out mice with human apoE isoform knock-in mice (Fryer et al., 2005a). While the effects of LRP1 on APP and Aβ have been thoroughly investigated, the potential implication of LDLR in AD pathogenesis has not been extensively studied. Interestingly, a couple of SNPs in the LDLR gene were found to be associated with a risk of AD in a gender specific manner (Lämsä et al., 2008; Zou et al., 2008). In addition, LDLR deficiency was associated with increased amyloid deposition in Tg2576 APP transgenic mice (Cao et al., 2006). In contrast, another study using PDAPP transgenic mice demonstrated that there was no alteration in Aβ levels at both a young and old age by biochemical analyses, although there was a trend toward increased amyloid burden in the absence of LDLR (Fryer et al., 2005a). It remains unknown whether increased levels or function of LDLR would have a direct effect on Aβ clearance or amyloid formation *in vivo*. Such knowledge will be critical to evaluate whether the modulation of LDLR expression and its stability can be exploited as a therapeutic target.

Lipoprotein receptor with 11 binding repeats (LR11, also known as Sorting protein-related receptor with LDLR class A-type repeats SorLA or SorL1)

LR11/SorLA was initially identified as a novel receptor capable of binding to the LRP-1 ligand receptor-associated protein (RAP) (Jacobsen et al., 1996). In addition to the ligand-binding complement-type repeats found in other LDL receptor family members, LR11/SorLA also has a vacuolar protein sorting 10 protein (vps10p) domain that is implicated in intracellular protein trafficking. Therefore, LR11/SorLA is considered as a unique hybrid protein that belongs to both the vps10p domain receptor family and the LDL receptor family. LR11/SorLA is predominantly expressed in neurons (Motoi et al., 1999). Its role in AD pathogenesis was initially suggested after the discovery of lower levels of LR11/SorLA expression in patients with sporadic AD (Scherzer et al., 2004) and mild cognitive impairment (Sager et al., 2007). Genetic association of LR11/SorLA variants with AD further corroborates its mechanistic link to AD pathogenesis (Rogaeva et al., 2007). LR11/SorLA sequesters APP in the trans-Golgi network, decreasing the amount of APP in post-Golgi compartments and the plasma membrane (Andersen et al., 2005; Schmidt et al., 2007). Consistent with the previous cell-based studies, reduction of LR11/SorLA protein levels increased Aβ levels and exacerbated amyloid plaque pathology in an APP/PSEN1Δ9 mouse model of amyloidosis (Dodson et al., 2008). Given such findings, it will be important to understand the factors that regulate LR11/SorLA protein levels.

Apolipoprotein receptor 2 (ApoER2, also known as LRP8)

ApoER2 is another member of the LDL receptor family that is highly expressed in the brain (Herz and Chen, 2006). Along with VLDLR, ApoER2 plays critical roles in neuronal migration and brain development by functioning as a receptor for reelin (Herz and Chen, 2006). ApoER2 also interacts with F-spondin through its extracellular ligand-binding complement-type repeats (Hoe et al., 2005b). F-spondin may function as a linker between ApoER2 and APP through its interaction with extracellular and intracellular domains of APP (Ho and Sudhof, 2004). Interactions of ApoER2 with APP are known to affect APP processing, leading to the increased production of Aβ (Fuentealba et al., 2007; He et al., 2007). However, it is not clear whether interactions between apoE and apoER2 in the CNS regulate apoE levels or function *in vivo*.

ATP-Binding Cassette Transporter A1 (ABCA1)

ATP-binding cassette A1 (ABCA1) is a cholesterol transporter widely expressed in several tissues, including the brain. It transports cellular cholesterol and phospholipids from cells to lipid-poor apolipoproteins, including apoE, in order to form high density lipoproteins (HDL) (Figure 2) (Lawn et al., 1999). Defects in the ABCA1 gene cause Tangier disease, which is

characterized by HDL deficiency in plasma, accumulation of cholesteryl esters in lymphatic tissue, peripheral neuropathy, and an increased risk for cardiovascular disease (Bodzioch et al., 1999;Brooks-Wilson et al., 1999;Rust et al., 1999). Because of its role in maintaining adequate cholesterol homeostasis and distribution, ABCA1 has gained attention as being an important protein target for both AD pathogenesis and treatment. Mouse studies have proven useful in clearly demonstrating an effect of ABCA1 on Aβ pathology. As expected, apoE from ABCA1 knock-out mice was very poorly lipidated both in the periphery and in the brain, compared to wild type mice. Genetic deletion of ABCA1 led to a significant reduction in steady-state apoE protein levels in the brain and CSF as well as in the plasma (Hirsch-Reinshagen et al., 2004;Wahrle et al., 2004), suggesting that poorly lipidated apoE is more rapidly catabolized. Due to the decreased levels of apoE, it was hypothesized that the lack of ABCA1 would lead to a decrease in Aβ deposition and amyloid formation in human APP mouse models. However, three independent studies demonstrated that ABCA1 deficiency leads to an increase in both Aβ and amyloid load in the brains of three different transgenic APP mouse models (Hirsch-Reinshagen et al., 2005;Koldamova et al., 2005;Wahrle et al., 2005). ABCA1 deletion did not have an effect on Aβ production (Koldamova et al., 2005;Wahrle et al., 2005), suggesting that the presence of poorly lipidated apoE somehow promotes the formation of amyloid fibrils. A recent *in vitro* study demonstrated that the presence of fully lipidated apoE was necessary for effective degradation of Aβ in microglia, suggesting that ABCA1 affects Aβ clearance via apoE (Jiang et al., 2008). The effect of increasing the level of ABCA1 in the mouse brain has also been investigated through the use of ABCA1 transgenic mice. When these mice, which had greater apoE lipidation, were crossed with PDAPP mice, there was a dramatic decrease in the amount of Aβ deposition and thioflavine-S positive plaques in the ABCA1 transgenic mice (Wahrle et al., 2008). This data suggests that increasing the lipidation state of apoE may influence either the metabolism of Aβ in the mouse brain or the ability of Aβ to form amyloid fibrils.

The Effect of ApoE on Synaptic Plasticity and Cognition

In vitro studies

In the peripheral and central nervous systems, the level of apoE increases following neuronal injuries. It has been hypothesized that such a surge of apoE may be required for repair of the nervous system by redistributing lipids and cholesterols for membrane repair and synaptic plasticity (Slezak and Pfrieger, 2003). Indeed, a number of studies suggest that apoE is important for maintenance of neuronal plasticity and function, particularly *in vitro* (Figure 1). The neurite outgrowth phenotype modulated by apoE isoforms is the most extensively studied in this regard. Most studies have shown that apoE3 augments neurite outgrowth to a greater extent than apoE4 (Bellosta et al., 1995; Nathan et al., 1994; Nathan et al., 2002; Sun et al., 1998; Teter et al., 1999). However, the effect of apoE4 on neurite outgrowth has been inconsistent among studies (DeMattos et al., 1998; Puttfarcken et al., 1997; Teter et al., 2002). The relative effect of the apoE2 isoform on neurite sprouting has not been thoroughly examined in most studies. The differences in cell types, lipid source, and growth factors in cell culture media might contribute some of the discrepancies between studies. The stimulation of neurite outgrowth by apoE may be mediated by LRP1 (Fagan et al., 1996; Holtzman et al., 1995; Narita et al., 1997; Nathan et al., 2002) or other apoE receptors (DeMattos et al., 1998; Puttfarcken et al., 1997). The isoform-specific effect of apoE on neurite outgrowth could be secondary to its effect on microtubule organization, since the inhibitory effect of apoE4 on neurite outgrowth was closely associated with its detrimental effect on microtubule stability (Nathan et al., 1995).

In vivo studies

Although the mechanisms by which apoE exerts isoform-specific differences on neurite outgrowth *in vitro* are interesting, it is critical to understand whether such findings are relevant *in vivo*. Some results obtained from *in vivo* studies appear to be consistent with *In vitro* findings. Compared with apoE3 transgenic mice, apoE4 transgenic mice had impaired compensatory sprouting and synaptogenesis after entorhinal cortex lesion (White et al., 2001) and were more severely impaired in learning and memory (Hartman et al., 2001; Raber et al., 1998; Raber et al., 2000). Some phenotypic differences observed with apoE transgenic mouse models have been replicated with apoE knock-in mouse models (Bour et al., 2008; Grootendorst et al., 2005; Trommer et al., 2004; Wang et al., 2005). In the presence of high levels of Aβ and APP, several studies have also demonstrated that apoE isoforms have differential effects on synaptic plasticity and cognition, even independent of plaque formation. Male apoE4 mice had significant deficits in spatial memory, whereas apoE3 prevented Aβ or APP-induced cognitive impairment (Raber et al., 2000). Support for the neuroprotective function of apoE2 against Aβ-mediated toxicity came from a study where apoE2 transgenic mice were bred with two different kinds of APP transgenic mice (Lanz et al., 2003). Dendritic spine loss observed in the hippocampus of young APP transgenic mice was ameliorated by apoE2 over-expression. While almost all *in vivo* studies have found that apoE3 augmented synaptic plasticity and exerted neuroprotective effects to a greater extent, compared with apoE4, the effects of apoE4 on synaptic plasticity were inconsistent among studies. Some studies propose that apoE4 has negative effects on neurites and synaptic functions (Cambon et al., 2000), whereas other findings suggest minor beneficial effects in apoE4 mice compared with apoE knock-out mice (Masliah et al., 1997; Veinbergs et al., 1999). Such conflicting observations from animal studies appear to reflect the inconsistent results obtained from *in vitro* experiments. In addition, findings from human subjects are not conclusive in regard to the effects of apoE on neuronal processes (Arendt et al., 1997; Schonheit et al., 2007). Further studies are warranted to determine whether there are apoE isoform-specific differences in synaptic structure and cognitive functions from subjects without obvious AD-related pathology.

The Role of ApoE in Neurotoxicity

In addition to modulating synaptic function, apoE4 may contribute to neuronal degeneration processes either by direct neurotoxicity or by indirectly potentiating detrimental effects of other insults, such as high levels of Aβ (Figure 1). One of the most extensively investigated direct toxic mechanisms involves the 29 kDa carboxyl-terminal-truncated fragment of apoE4 (amino acid 1–272 residues) (Mahley et al., 2007;Mahley et al., 2006). The 29 kDa amino-terminal fragment generated by chymotrypsin-like serine protease has been shown to induce cytoskeletal disruptions and perturb mitochondrial energy balance. Additionally, the 22 kDa amino-terminal fragment produced by thrombin cleavage (amino acid 1dues) also has neurotoxic effects (Tolar et al., 1999). Since the existence of 22 kDa apoE fragments in the human brain has not been conclusively demonstrated, the relevance of the thrombin cleavage fragment to AD pathogenesis remains unclear. Along with Aβ-independent intrinsic toxicities, apoE4 has been shown to exacerbate neurotoxicity triggered by A and other insults (Mahley et al., 2006). Whether apoE amino-terminal fragments play a role in the brain *in vivo* is not yet clear and further studies are required to define its potential role in the normal brain and in AD pathogenesis.

The Effect of ApoE Isoforms on Tau

Along with amyloid plaque formation, hyperphosphorylation of the microtubule-binding protein tau and subsequent formation of neurofibrillary tangles are hallmarks of AD pathology. The relationship between apoE and tau has not been thoroughly investigated and

the results are much less clear than the association between apoE ε4 allele dose and amyloid plaque burden. Although some studies reported a positive relationship between the neurofibrillary tangle density and apoE ε4 allele dosage (Ghebremedhin et al., 1998; Nagy et al., 1995; Ohm et al., 1995; Polvikoski et al., 1995), others found no clear correlation (Itoh and Yamada, 1996; Landen et al., 1996b; Morris et al., 1995; Olichney et al., 1996; Oyama et al., 1995). Unlike studies with human subjects, data from *in vitro* and animal models appear to be more consistent among studies. Under *in vitro* conditions, apoE3 binds tightly to tau and forms an SDS-stable complex through the interaction of the N-terminal domain of apoE3 and the microtubule-binding repeat regions of tau, whereas apoE4 does not interact significantly with tau (Strittmatter et al., 1994). The interaction between apoE3 and tau was prevented by the phosphorylation of tau, suggesting that apoE3 binds preferentially to non-phosphorylated tau. However, there is currently no conclusive evidence demonstrating localization of apoE to the neuronal cytosol, where the majority of tau exists under normal conditions (DeMattos et al., 1999). Therefore, the physiological relevance of the direct interaction between apoE and tau remains to be determined. Of note, more recent data suggests the possibility that a fragment of apoE4 (1–272 amino acids), but not full-length apoE4, escapes the secretory pathway, translocates to the cytosolic compartment, and interacts with cytoskeletal components, including tau and neurofilament (Chang et al., 2005). Alternatively, the effects of apoE on tau phosphorylation could be explained by an intracellular signaling pathway induced by apoE (Harris et al., 2004; Hoe et al., 2005a), rather than the direct interaction between apoE and tau. Although *in vitro* studies have provided some insights, *in vivo* studies proving whether an apoE-isoform dependent effect on tau even exists will be critical.

The Role of ApoE in Neuroinflammation

Inflammation and apoE

Abnormal activation of astrocytes and microglia are common pathological features of many neurodegenerative diseases. Along with amyloid plaques and neurofibrillary tangles, prominent activation of innate inflammatory responses is also observed in the brains of AD patients. Such neuroinflammation is generally believed to contribute to the pathogenesis of AD (Figure 1) (Bales et al., 2000). Activated glial cells are closely associated with amyloid plaques, suggesting that plaques or soluble forms of Aβ around plaques, may induce inflammatory cascades. Consistent with neuropathological findings, Aβ is shown to trigger glial neuroinflammatory responses in cell culture systems (Hu et al., 1998). Interestingly, Aβ induces the production of apoE and the increased levels of apoE limit Aβ-driven neuroinflammation, possibly functioning as a feedback mechanism (Guo et al., 2004;LaDu et al., 2001). In addition, innate inflammatory responses are also modulated by apoE and LRP1, implying that apoE may have general anti-inflammatory effects (LaDu et al., 2000b). It is tempting to speculate that the interaction and subsequent co-deposition of Aβ with apoE might serve to compromise the anti-inflammatory function of apoE by reducing the functionally available pool size of apoE, eventually leading to chronic neuroinflammation. Consistent with the anti-inflammatory role of apoE *in vitro*, lack of apoE expression in mice was associated with increased inflammation, including induction of several cytokines and pro-inflammatory responses, in response to treatment of Aβ and other activating stimuli (LaDu et al., 2001;Lynch et al., 2001). Glial activation and subsequent apoE induction appear to be mediated, at least in part, by the nuclear factor-κb (NF-κb) transcription factor (Bales et al., 2000).

ApoE isoforms and neuroinflammation

If there are apoE isoform-dependent differences in the anti-inflammatory function of apoE *in vivo*, such differences might in part explain the differential risk for AD caused by apoE

isoforms. In support of this hypothesis, several studies demonstrated that exogenously applied apoE4 has more robust pro-inflammatory activity than apoE3 in astrocytes and microglial cells (Barger and Harmon, 1997; Guo et al., 2004). In addition, apoE isoform-specific effects on neuroinflammation have been studied *in vivo* with human apoE knock-in mice. After intravenous administration of LPS, apoE4 knock-in mice had greater inflammatory responses compared with apoE3 knock-in mice (Colton et al., 2004; Lynch et al., 2003). Taken together, these data suggest that apoE4 may have pro-inflammatory or less effective anti-inflammatory function and therefore may exacerbate or inefficiently prevent the detrimental neuroinflammation in AD, compared with the apoE3 isoform. However, it is still not known whether apoE2 modulates any inflammatory process triggered by Aβ. Although it is interesting to note that apoE is involved in the presentation of exogenous lipid antigens (van den Elzen et al., 2005), how apoE exerts its effects on immune responses still remains unclear. The role of apoE in the inflammation associated with AD pathogenesis needs to be further investigated with genetic and pharmacological manipulations of specific inflammatory pathways.

The Effect of ApoE on Metabolic Alterations in the Brain

Despite the steady effort to link apoE with the specific disease pathogenesis of AD within the brain, the possibility remains that apoE indirectly affects AD onset and progression by modulating the function of the cerebrovascular system. The apoE4 isoform has been linked with increased levels of LDL and has been demonstrated to be a risk factor for cardiovascular disease (Song et al., 2004; Wilson et al., 1994). As a result, increased levels of atherosclerosis associated with apoE4 (Elosua et al., 2004; Graner et al., 2008) could have detrimental effects on brain function through decreased blood flow and altered metabolic properties. Positron emission tomography (PET) studies have shown that AD brains exhibit decreased glucose metabolism in distinct regions (Alexander et al., 2002; Minoshima et al., 1995). Furthermore, studies looking at both young and old non-demented carriers of the apoE4 isoform observed a similar regional pattern of hypometabolism prior to the onset of disease that correlates with the changes seen in the AD brain. This suggests the possibility that an apoE-related decrease in brain metabolism may contribute to development of AD (Reiman et al., 1996; Reiman et al., 2004, 2005; Small et al., 2000). Whether these observations in apoE4 individuals are due to a direct effect of apoE4 on brain metabolism or simply an indirect effect of the early stages of apoE4-induced early amyloid formation with resulting decreased synaptic activity and brain metabolism remains to be determined. Therefore, further studies will be important to clarify the role of apoE4-related decreased brain metabolism and whether the presence of apoE4 directly promotes the metabolic changes that occur during the disease process or it indirectly affects brain metabolism via effects on amyloid or possibly effects on the cerebrovasculature.

Concluding Remarks

Prevailing data suggests that the main effect of apoE isoforms on risk for AD is via the effect of apoE on Aβ metabolism, influencing the time of onset of Aβ deposition in both brain parenchyma and vasculature (Figure 1). By influencing the onset, location, and amount of Aβ aggregation in the brain, this is then likely to trigger a set of downstream events that ultimately culminates in AD, CAA, or both. Since apoE modulates not only clearance but also aggregation of Aβ as well as other neuropathological changes, it has been difficult to elucidate the exact pathological mechanism behind the observed Aβ phenotypes in human and animal studies. A critical but still unresolved question is whether the apoE ε4 allele influences AD pathogenesis, by a gain of toxic function, a loss of protective function, or a combination of both. A similar issue regarding the role of PSEN mutations in AD has been debated recently (Bentahir et al., 2006;Shen and Kelleher, 2007;Winklhofer et al., 2008).

Due to conflicting pathogenic mechanisms of apoE4 in AD, two different therapeutic strategies are currently being considered; one trying to decrease the toxic effects of apoE4 by altering its structure and the other attempting to restore the physiological functions of apoE/apoE4 by increasing its expression and function. In addition, influencing the lipidation of apoE as well as targeting apoE receptors such as LDLR and LRP is also a potential strategy for future therapeutic design. Further studies are warranted to tease out how much Aβ versus non-Aβ mediated effects of apoE influence AD.

Acknowledgments

This work was supported by NIH grants AG13956 (DMH) and grants from the American Health Assistance Foundation (DMH and JK). We would like to thank Dr. John R. Cirrito for critical reading of the manuscript.

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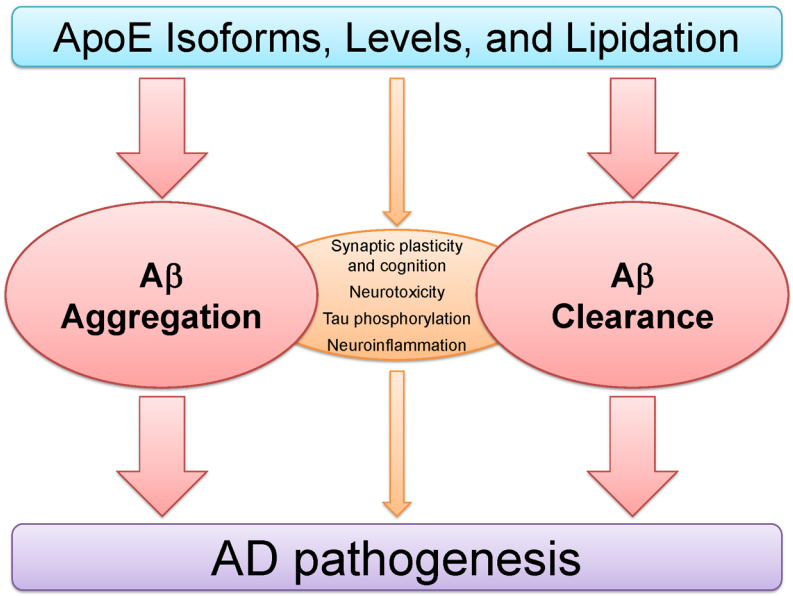

Figure 1. Pathogenic Mechanisms of ApoE in Alzheimer's Disease

Several mechanisms have been proposed to understand the differential effects of apoE isoforms on AD pathogenesis. Evidence suggests that the major effect of apoE isoforms on the risk of developing AD is via its effect on Aβ aggregation and clearance, influencing the onset of Aβ deposition. Other mechanisms, including the effects of apoE isoforms on synaptic function, neurotoxicity, tau hyper-phosphorylation, and neuroinflammation, may also contribute to the disease process. Independent of *APOE* genotype, differences in the apoE levels and lipidation state may also mediate processes involved in AD pathogenesis.

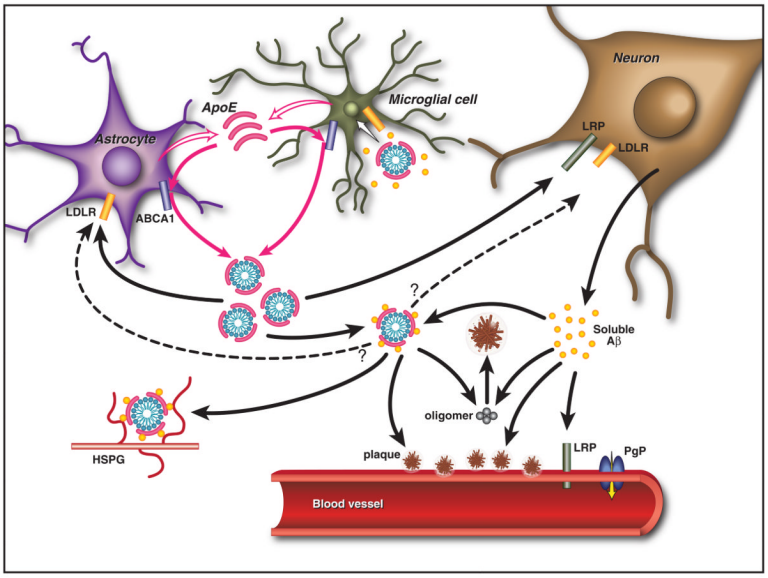

Figure 2. Effects of ApoE on Aβ Metabolism and Deposition

ApoE is primarily produced by both astrocytes and microglia and is subsequently lipidated by ABCA1 to form lipoprotein particles. In the extracellular space, lipidated apoE binds to soluble Aβ in an isoform-dependent pattern (E2>E3>E4) and influences the formation of parenchymal amyloid plaques and transport of Aβ within the CNS. ApoE is endocytosed into various cell types within the brain by different members of the LDL receptor family, including LDLR and LRP1. ApoE may also facilitate the cellular uptake of Aβ through the endocytosis of a complex of apoE-containing lipoprotein particles bound to Aβ in a manner that likely depends upon the isoforms and its level of lipidation. Furthermore, apoE has been shown to directly enhance both the degradation of Aβ within microglial cells and the ability of astrocytes to clear diffuse Aβ deposits (Jiang et al., 2008; Koistinaho et al., 2004). Aβ associated with apoE-containing lipoprotein particles may also be retained within the CNS through their binding to heparin sulfate proteoglycan (HSPG) moieties present in the extracellular space (Mahley and Rall, 2000). At the BBB, soluble Aβ is predominantly transported from the interstitial fluid into the bloodstream via LRP1 and P-glycoprotein (Cirrito et al., 2005; Zlokovic, 2008). ApoE has been shown to slow the transport of Aβ across the BBB in an isoform-dependent manner (E4>E3>E2) (Bell et al., 2007; Deane et al., 2008; Ito et al., 2007). In addition, apoE can influence the pathogenesis of CAA in an APP transgenic mouse model, with apoE4 increasing the amount of vascular plaques in comparison to apoE3 (Fryer et al., 2005b).